Reducing the Need for Antimicrobials—
Critical Research and Development Actions

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The opinions expressed in this presentation are my own, and do not represent those of Cepheid, DMDP, or Stanford University.
• What is the value of investing in diagnostics?

Suspect patients in holding area wait for up to 8 days for results from distant reference laboratory.
• What difference can it make?

a. Ability to make accurate diagnosis at point of intervention/impact and inform pt. management (TAT from 1 week to 2 hours)

b. Patients not placed at risk if not infected

c. Reduced risk of infection for the HCW and lab worker

d. Increased specificity – 2 targets (help differentiate vaccine strain from WT)

e. SAC to assure sufficient patient sample (buccal swab); blood (fewer false negatives)

f. Longer term testing of semen, breast milk, etc. for ongoing monitoring
Use of Xpert MTB/RIF in Decentralized Public Health Settings and Its Effect on Pulmonary TB and DR-TB Case Finding in India

Kuldeep Singh Sachdeva¹, Neeraj Raizada²*, Achuthan Sreenivas³, Anna H. van’t Hoog⁴, Susan van den Hof⁴,⁵, Puneet K. Dewan⁶, Rahul Thakur², R. S. Gupta¹, Shubhangi Kulsange², Bhavin Vadera², Ameet Babre², Christen Gray⁷, Malik Parmar³, Mayank Ghedia¹, Ranjani Ramachandran², Umesh Alavadi², Nimalan Arinaminpathy⁸, Claudia Denkinger², Catharina Boehme², C. N. Paramasivan²

“Compared with the baseline strategy of selective DST only for PTB cases at high risk of drug-resistant TB, Xpert MTB/RIF implementation increased rifampicin resistant TB case detection by over five-fold.”

Sachdeva et al. PLoS ONE 2015
Development, roll-out and impact of Xpert MTB/RIF for tuberculosis: what lessons have we learnt and how can we do better? Albert et al. 2016

GeneXperts now in 122 of 145 eligible countries

The global roll-out of Xpert MTB/RIF has changed the diagnostic landscape of tuberculosis (TB). More than 18 million tests have been performed in 122 countries since 2011, and detection of multidrug-resistant TB has increased three to eight-fold compared to conventional testing.

The roll-out has galvanised stakeholders, from donors to civil society, and paved the way for universal drug susceptibility testing.

But in most studies, no difference in mortality and in some studies, cost of Xpert rollout was higher or only cost-neutral.

Why?
The same system inadequacies already discussed yesterday. (Dr. Linder was right !)
What type of Dx should be prioritized? (4 themes)

a. Tests for which immediate patient management decisions will impact (1) public health and (2) individual patient outcomes

<table>
<thead>
<tr>
<th></th>
<th>Antenatal Test</th>
<th>Intrapartum Test</th>
</tr>
</thead>
<tbody>
<tr>
<td># Term deliveries</td>
<td>2,761</td>
<td>2,814</td>
</tr>
<tr>
<td>GBS colonization rate</td>
<td>11.7%</td>
<td>16.7%</td>
</tr>
<tr>
<td>Cost of delivery &amp; Rx newborns</td>
<td>$146,057</td>
<td>$25,433</td>
</tr>
<tr>
<td>Probability neonatal GBS disease</td>
<td>0.9%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Probability of GBS given negative GBS screening</td>
<td>0.6%</td>
<td>0.17%</td>
</tr>
<tr>
<td># Women received IAP</td>
<td>311</td>
<td>436</td>
</tr>
<tr>
<td>*Avg Total cost per delivery</td>
<td>$1,759</td>
<td>$1,754</td>
</tr>
</tbody>
</table>

Group B streptococcal EO neonatal disease

Cost and Effectiveness of Intrapartum Group B Streptococcus Polymerase Chain Reaction Screening for Term Deliveries

A Randomized Controlled Trial Comparing the Treatment of Patients Tested for Chlamydia and Gonorrhea After a Rapid Polymerase Chain Reaction Test Versus Standard of Care Testing

Larissa May, MD,* Chelsea E. Ware, MS;† Jeanne A. Jordan, PhD;† Mark Zocchi, MPH;‡§ Catherine Zatorski, BA;† Yasser Ajabnoor, MD;† and Jesse M. Pines, MD‡§

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Test</th>
<th>Control</th>
<th>% Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Patients (N=70)</strong></td>
<td>N=43</td>
<td>N=27</td>
<td></td>
</tr>
<tr>
<td>Empiric treatment for CTNG</td>
<td>12 (27.9)</td>
<td>17 (63.0)</td>
<td>-35.1</td>
</tr>
<tr>
<td>Mean total charges (SD)</td>
<td>$2,498 (912)</td>
<td>$3,086 (1,742)</td>
<td>-$588</td>
</tr>
<tr>
<td><strong>With Negative Test Results (N=57)</strong></td>
<td>N=38</td>
<td>N=19</td>
<td></td>
</tr>
<tr>
<td>Empiric treatment for CTNG</td>
<td>8 (21.1)</td>
<td>11 (57.9)</td>
<td>-36.8</td>
</tr>
<tr>
<td><strong>One week Follow-up (N=37)</strong></td>
<td>N=21</td>
<td>N=16</td>
<td></td>
</tr>
<tr>
<td>Subsequent hospitalization</td>
<td>1 (4.8)</td>
<td>1 (6.3)</td>
<td>-1.5</td>
</tr>
<tr>
<td>Subsequent office visit</td>
<td>5 (23.8)</td>
<td>2 (12.5)</td>
<td>11.3</td>
</tr>
<tr>
<td>Notified of results</td>
<td>17 (81.0)</td>
<td>4 (25.0)</td>
<td>56.0</td>
</tr>
<tr>
<td>Symptoms resolved</td>
<td>17 (81.0)</td>
<td>10 (62.5)</td>
<td>18.5</td>
</tr>
</tbody>
</table>
• What type of Dx should be prioritized?

b. Tests to rapidly identify patients eligible for clinical trials of new antimicrobial agents at enrollment

c. Rapid tests that would definitively rule out bacterial infection at patient presentation (prevent Abx use)

d. Rapid tests to detect resistance factors directly from patient samples or for screening/surveillance
Large hospital outbreak of KPC-2-producing *Klebsiella pneumoniae*: investigating mortality and the impact of screening for KPC-2 with polymerase chain reaction

Median time to contact isolation (days)

<table>
<thead>
<tr>
<th>Method</th>
<th>Median Time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPC PCR</td>
<td>1.5</td>
</tr>
<tr>
<td>Culture based Methods</td>
<td>5</td>
</tr>
</tbody>
</table>
Stevens et al. 2016. Cloud-Based Surveillance, Connectivity, and Distribution of the GeneXpert Analyzers for Diagnosis of Tuberculosis (TB) and Multiple-Drug-Resistant TB in South Africa. In book: Molecular Microbiology: Diagnostic Principles and Practice
Data and Images from Lesley Scott

Mtb PCR positive tests 2015

Rif Resist PCR tests 2015

Swaziland
• What are the challenges and needs to accelerate the development of these diagnostics?

  a. Lack of predictable profit (Ex: Ebola, Mtb/Rif)
  b. Clinical trials – cost, requirements, regulatory issues (review time, difficult demands)
  c. Final cost of product and market acceptability (need for outcomes studies; perceived ROI)
  d. Changing microbial genetics and epidemiology

• How might Drive-Dx idea help?

  a. Incentivize developers with guaranteed purchase agreements
  b. Make FDA more like CE (avoid adding stringency to CE mark requirements)
• What immediate steps can be taken for the greatest short term impact?

a. Publicize specific target product profiles
b. Create a rapid, inexpensive regulatory path to market, which may include abbreviated clinical trials and extensive post-market review/surveillance
c. Guarantee sufficient sales to offset development costs (pre-purchase agreements)